The present invention is directed to a compound represented by formula (I) or a pharmaceutically acceptable salt or solvate thereof. See Claim 1. An important feature of the claimed compounds is that they have a ***substituted phenylene group*** bonded to the N'-substituted urea group.

The rejection of the claims under 35 U.S.C. §102(a) over JP 11158149 is believed to be obviated by the certified English translation of the Japanese priority application submitted herewith. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejections of the claims under 35 U.S.C. §102(b) and §103(a) over WO 97/17329 (part of same patent family as U.S. 6,143,764) are respectfully traversed. This reference does not describe or suggest the claimed compounds. Following the Examiner's lead, all citations refer to U.S. '764.

The Examiner's attention is directed to formula (V) at the top of column 4. Please note that the phenyl ring does not contain any additional substituents. In all of the many compounds exemplified in this patent, the phenyl ring carries no additional substituents.

In contrast, Claim 1 of the present application explicitly recites that R^5, R^6, R^7, and R^8 do not simultaneously represent a hydrogen atom. Therefore, the compounds described in the reference cannot overlap with those claimed, because the positions which correspond to R^5, R^6, R^7, and R^8 in the compounds described in the reference all simultaneously represent a hydrogen atom. Accordingly, the reference fails to anticipate the claims, and withdrawal of this ground of rejection is respectfully requested.

Moreover, the reference certainly fails to suggest the claimed compounds. The reference explicitly teaches the phenyl ring shown in formula (V). The reference explicitly depicts the structure as showing no additional substituents on that ring. Furthermore, the reference describes many examples of such compounds, all of them which lack any additional substituents on the phenyl ring. Based on this disclosure in the reference, one reading the

reference would not be motivated to prepare the claimed compounds. Therefore, the reference fails to suggest the claimed compounds. In addition, the inventors have discovered that the claimed compound have angiogenesis inhibitory activity, which is not described in the reference.

Based on the foregoing, the claimed compounds are neither anticipated by nor obvious over WO 97/17329. Withdrawal of these grounds of rejection is respectfully requested.

The rejection of the claims under 35 U.S.C. §112, first paragraph, is respectfully traversed.

At page 3, line 11 through page 4, line 12 of the Official Action, the Examiner alleges that it is not possible that a compound is effective against cancer generally. The present compounds are a new type of anticancer agents. Specifically, the claimed compounds have angiogenesis inhibitory activity. All cancer cells receive their nutrient supply through newly-generated capillary vessels so that the cancer cells can maintain their lives and proliferate.

As stated on page 27, lines 25 to 35 and page 29, line 28 through page 30, line 23 of the present specification, when the present compounds are administered to the body, the nutrient supply route to the cancer cells is effectively cut off and the cancer cells will then regress and, possibly, disappear. It is believed that this treatment mechanism would apply to malignant tumors generally. Further, Example 4 demonstrates that the tumor growth can be actually inhibited in nude mice by administering the present compounds orally or intraperitoneally. Given these results, it is believed that those skilled in the art reading the specification would appreciate that the present compounds can be used as anticancer agents generally.

At page 4, line 22 through page 5, line 11 of the Official Action, the Examiner stated that the specification does not reasonably provide enablement for solvates. Once new

compounds are provided, one skilled in the art can produce their solvates because the basic skill of producing solvates was well known in the art at the time the present application was filed. As evidence thereof, journal articles are attached which show that chloride methanol solvates of quinazoline derivatives can be produced.

In view of the foregoing, the claims are enabled. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of the claims under 35 U.S.C. §112, second paragraph, is believed to be obviated by the amendments submitted above in part and is, in part, respectfully traversed. The following paragraphs refer to the Examiner's comments at pages 2-3 of the Official Action dated May 15, 2002.

1. First, the term "heterocyclic" is not indefinite at all. As the Examiner no doubt recognizes, a heterocyclic group is a cyclic group which contains a heteroatom. This is elementary organic chemistry. A copy of page 1179 of an undergraduate organic chemistry text (*Organic Chemistry*, K. Peter C. Vollhardt, W.H. Freeman, New York, 1987) is submitted herewith. Page 1179 is the first page of the chapter entitled "Heterocycles, Heteroatoms in Cyclic Organic Compounds," and clearly defines the term "heterocyclic." In addition, the claims specify that the group may be saturated or unsaturated and has a recited number of carbon atoms. Accordingly, one skilled in the art reading the claims will readily appreciate the metes and bounds of the recited heterocyclic groups.

2. This issue has been addressed by amendment.

3. This issue has been addressed by amendment.

4. Claim 50 has been canceled.

5. Referring to the specification at page 30, lines 12-15, the "target blood vessels" are blood vessels which involve nutrient supply for tissues which cause disease, specifically, blood vessels close to tissues to be treated.

Based on the foregoing, the claims are definite within the meaning of 35 U.S.C. §112, second paragraph. Withdrawal of this ground of rejection is respectfully requested.

The Examiner has inquired as to whether there are U.S. applications which correspond to WO 01/47890 or JP 11158149. U.S. Application Serial No. 10/168,392 corresponds to WO 01/47890. No U.S. application corresponding to JP 11158149 has been filed.

Regarding the Restriction Requirement and the rejection for "improper Markush," the Examiner has noted that one of the rings is variable. However, all of the claimed compounds carry a substituted phenylene group bonded to the N'-substituted urea group, as discussed above, and the Examiner has not shown that that structure does not define over the art. Accordingly, the Examiner should examine the pending claims without restriction.

Applicants submit that the present application is in condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

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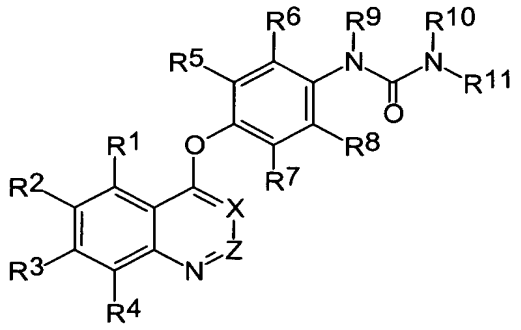
Marked-Up Copy
Serial No: 09/889,858
Amendment Filed on: HEREWITH

IN THE CLAIMS

Claims 49 and 50 (Cancelled).

Please amend the claims as shown in the attached marked-up copy to read as follows:

--1. (Amended) A compound represented by formula (I) or a pharmaceutically acceptable salt or solvate thereof:



(I)

wherein

X and Z each represent CH or N;

R^1, R^2, and R^3, which may be the same or different, represent a hydrogen atom, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, nitro, or amino, which C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted by a halogen atom; hydroxyl; C_{1-4} alkoxy; C_{1-4} alkoxycarbonyl; amino on which one or two hydrogen atoms are optionally substituted by C_{1-4} alkyl optionally substituted by hydroxyl or C_{1-4} alkoxy; group $R^{12}R^{13}N$-C(=O)-O- wherein R^{12} and R^{13}, which may be the same or different, represent a hydrogen atom or C_{1-4} alkyl which alkyl is optionally substituted by hydroxyl or C_{1-4} alkoxy; or group

R^{14}-(S)m- wherein R^{14} represents a saturated or unsaturated three- to seven-membered carbocyclic or heterocyclic group optionally substituted by C_{1-4} alkyl and m is 0 or 1;

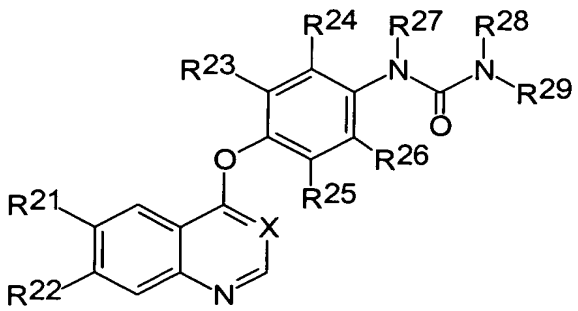
R^4 represents a hydrogen atom;

R^5, R^6, R^7, and R^8, which may be the same or different, represent a hydrogen atom, a halogen atom, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, nitro, or amino, provided that R^5, R^6, R^7, and R^8 do not simultaneously represent a hydrogen atom;

R^9 and R^{10}, which may be the same or different, represent a hydrogen atom, C_{1-6} alkyl, or C_{1-4} alkylcarbonyl, the alkyl portion of which C_{1-6} alkyl or C_{1-4} alkylcarbonyl is optionally substituted by a halogen atom; C_{1-4} alkoxy; amino which is optionally substituted by C_{1-4} alkyl optionally substituted by C_{1-4} alkoxy; or a saturated or unsaturated three- to seven-membered carbocyclic or heterocyclic group; and

R^{11} represents C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl (which C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl each are optionally substituted by a halogen atom or C_{1-6} alkoxy), or R^{15}-(CH_2)n- wherein n is an integer of 0 to 4 and R^{15} represents a saturated or unsaturated three- to seven-membered carbocyclic or heterocyclic group which is optionally substituted by a halogen atom, C_{1-6} alkyl, or C_{1-6} alkoxy and is optionally condensed with <u>another</u> [other] saturated or unsaturated three- to seven-membered carbocyclic ring or heterocyclic ring to form a bicyclic ring.

5. (Amended) A compound represented by formula (Ia) or a pharmaceutically acceptable salt or solvate thereof:



(Ia)

wherein

X represents CH or N;

R^{21} and R^{22}, which may be the same or different, represent unsubstituted C_{1-6} alkoxy or group R^{31}-(CH_2)p-O- wherein R^{31} represents a halogen atom, hydroxyl, C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl, amino on which one or two hydrogen atoms are optionally substituted by C_{1-4} alkyl optionally substituted by hydroxyl or C_{1-4} alkoxy, group $R^{12}R^{13}$N-C(=O)-O- wherein R^{12} and R^{13}, which may be the same or different, represent a hydrogen atom or C_{1-4} alkyl which alkyl is optionally substituted by hydroxyl or C_{1-4} alkoxy, or group R^{14}-(S)m- wherein R^{14} represents a saturated or unsaturated three- to seven-membered carbocyclic or heterocyclic group optionally substituted by C_{1-4} alkyl and m is 0 or 1; and p is an integer of 1 to 6;

R^{23}, R^{24}, R^{25}, and R^{26}, which may be the same or different, represent a hydrogen atom, a halogen atom, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, nitro, or amino, provided that R^{23}, R^{24}, R^{25}, and R^{26} do not simultaneously represent a hydrogen atom;

R^{27} and R^{28}, which may be the same or different, represent a hydrogen atom, C_{1-6} alkyl, or C_{1-4} alkylcarbonyl, the alkyl portion of which C_{1-6} alkyl or C_{1-4} alkylcarbonyl is optionally substituted by a halogen atom; C_{1-4} alkoxy; amino which is optionally substituted by C_{1-4} alkyl optionally substituted by C_{1-4} alkoxy; or a saturated or unsaturated three- to seven-membered carbocyclic or heterocyclic group; and

R^{29} represents C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl (which C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl each are optionally substituted by a halogen atom or C_{1-4} alkoxy), or R^{32}-(CH_2)q- wherein q is an integer of 0 to 4 and R^{32} represents a saturated or unsaturated six-membered carbocyclic or heterocyclic group which is optionally substituted by a halogen atom, C_{1-4} alkyl, or C_{1-4} alkoxy and is optionally condensed with another [other] saturated or

unsaturated five- or six-membered carbocyclic ring or heterocyclic ring to form a bicyclic ring.

51. (Twice Amended) A method for treating a disease selected from the group consisting of malignant tumor, diabetic retinopathy, chronic rheumatism, psoriasis, and atherosclerosis, [and Kaposi's sarcoma,] comprising the step of administering an effective amount of the compound according to claim 1 or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable carrier, to mammals.

Claims 53-59 (New).--

LIST OF RELATED CASES

Docket Number	Serial or Patent No.	Filing or Issue Date	Status or Patentee
224541US0 PCT	10/168,392	06/21/02	PENDING
UNKNOWN	5,480,883	01/02/96	SPADA, et al.
221969US0 PCT*	09/889,858	07/23/01	PENDING

*Present application; listed for information.